concluded that the claimed invention was clearly anticipated.

Claims 2, 8, 10, 11-22, 29-32, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draget et al (1991) as applied to claims 1, 3-7, 9, 23-28, and 33-36 above, and further in view of Hauselmann et al (US Patent 5,658,343) and Cao et al (1996).

The Examiner stated that Applicant's invention includes a calcium ion to carboxyl molar ratio of 0.27, .09 to .9, or .18 to .72; and the swelling of the hydrogel as a function of the calcium ion concentration. The method may also comprise the addition of cells in vitro, such as osteoblasts, and for the implantation of the product.

The Examiner stated that Draget does not teach the use of cells in the method, a method of tissue engineering, the implantation of the gel, or the ratio of calcium ions to carboxyl groups. She further stated that Hauselmann '343 teaches the method of producing an alginate gel in vitro comprising cells that produce an extracellular matrix, for implantation in vivo. She stated that Hauselmann also teaches that the molar ratio of calcium ions to carboxyl groups in the gel determines the amount of crosslinking of the gel, as well as the amount of swelling, and thus the size of the gel. The Examiner stated that Cao teaches the method of making and using biodegradable calcium alginate gels with osteoblasts in vitro for implantation in vivo to generate bone growth.

Therefore, the Examiner concluded that, in light of Draget, Hauselmann '343 and Cao, it would have been obvious to the skilled artisan to add cells, such as osteoblasts, to the composition disclosed by Draget. She stated that one would have been motivated to do this to utilize the gel as a scaffold for cell growth and differentiation, otherwise known as tissue engineering, both in vitro for implantation, or for injection and

solidification in vivo, such as taught by Hauselmann and Cao. She also stated that one would have been motivated to alter the calcium ion concentration and the ratio of calcium ions to alginate carboxyl groups in order to alter the amount of water binding to the matrix, and hence the amount of gel swelling and size of the gel, because Hauselmann '343 discloses that this procedure is widely known and used in the art of hydrogels. Thus, the Examiner concluded that the claimed invention of claims 10, 21, 22, 29-32, 37 and 38 pertaining to specific ion concentrations and molar ratios resulting in hydrogel swelling and shrinking are result effective variables which could readily have been determined by one of ordinary skill in the art.

Applicant's invention as defined in independent claims 1, 23 and 34 has been amended herein to include the step of selectively controlling the hydrogel system to a predetermined size by varying a calcium ion/cation concentration of a medium into which the hydrogel system is introduced (claims 1 and 23); or to include cells incorporated into the hydrogel composition, thereby forming a hydrogel/cell system. Since Draget does not teach either this step or the inclusion of cells, it is submitted that Applicant's invention as defined in these claims, as well as any dependent therefrom, has traversed and overcome the § 102(e) rejection.

None of the cited references teach or suggest selective size control of a hydrogel system by varying cation concentration of a medium into which it is introduced. The '343 patent controls the hydrogel system by a **mechanical means** (the boundary layers). The passage referred to by the Examiner (Col. 7, lines 29 et seq.) speaks of molar ratio of calcium ions to carboxyl groups **in the gel** to determine the amount of crosslinking--in sharp contrast, Applicant's invention as defined in claims 1, 11 and 23 recites selective control of the hydrogel system by varying cation/calcium ion

concentration **in the medium** into which the hydrogel is introduced. Claim 39 recites a culture medium having a predetermined cation concentration for maintaining the hydrogel/cell system. The amendment of these claims is fully supported by the specification as filed.

As such, it is submitted that Applicant's invention as defined in claims 1, 11, 23 and 39, as well as all claims dependent therefrom, is not anticipated, taught or rendered obvious by Draget, Cao or '343, either alone or in combination, and patentably defines over the art of record.

Claim 34 has been amended to recite cells incorporated into the hydrogel composition, thereby forming a hydrogel/cell system. None of the cited references teach such a system. Although Cao and '343 disclose an alginate mixed with a calcium compound and cells, neither of these references teach a system which includes a cation-releasing compound. Thus, it is submitted that Applicant's invention as defined in claim 34 and all claims dependent therefrom is not anticipated, taught or rendered obvious by Draget, Cao or '343, either alone or in combination, and patentably defines over the art of record.

Cao uses $CaSO_4$ as a calcium source to form crosslinks in alginate gels. This method (using $CaSO_4$) is presented in the subject application as a control method, which results in poor gel formation (irregular shape and heterogeneity) and inferior mechanical properties. Cao implanted his mixture *in vivo* without characterizing the structural homogeneity or mechanical properties. He has neither clearly presented the problems of his system, nor any solutions to them. Although the Draget paper had published way before his work, Cao (an expert in the field of tissue engineering, more than just ordinary skilled workers in the field), nor anyone else in the field has derived a combination of

the tissue engineering approach with Draget's homogeneous gelation approach thus far.

In summary, Claims 1-20 and 22-38 remain in the application. Claim 21 has been canceled. New claims 39-44 have been added in order to set forth additional specific embodiments of Applicant's invention. It is submitted that, through this amendment, Applicant's invention as set forth in these claims is now in a condition suitable for allowance.

Further and favorable consideration is requested. If the Examiner believes it would expedite prosecution of the above-identified application, she is cordially invited to contact Applicant's Attorney at the below-listed telephone number.

Respectfully submitted,

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